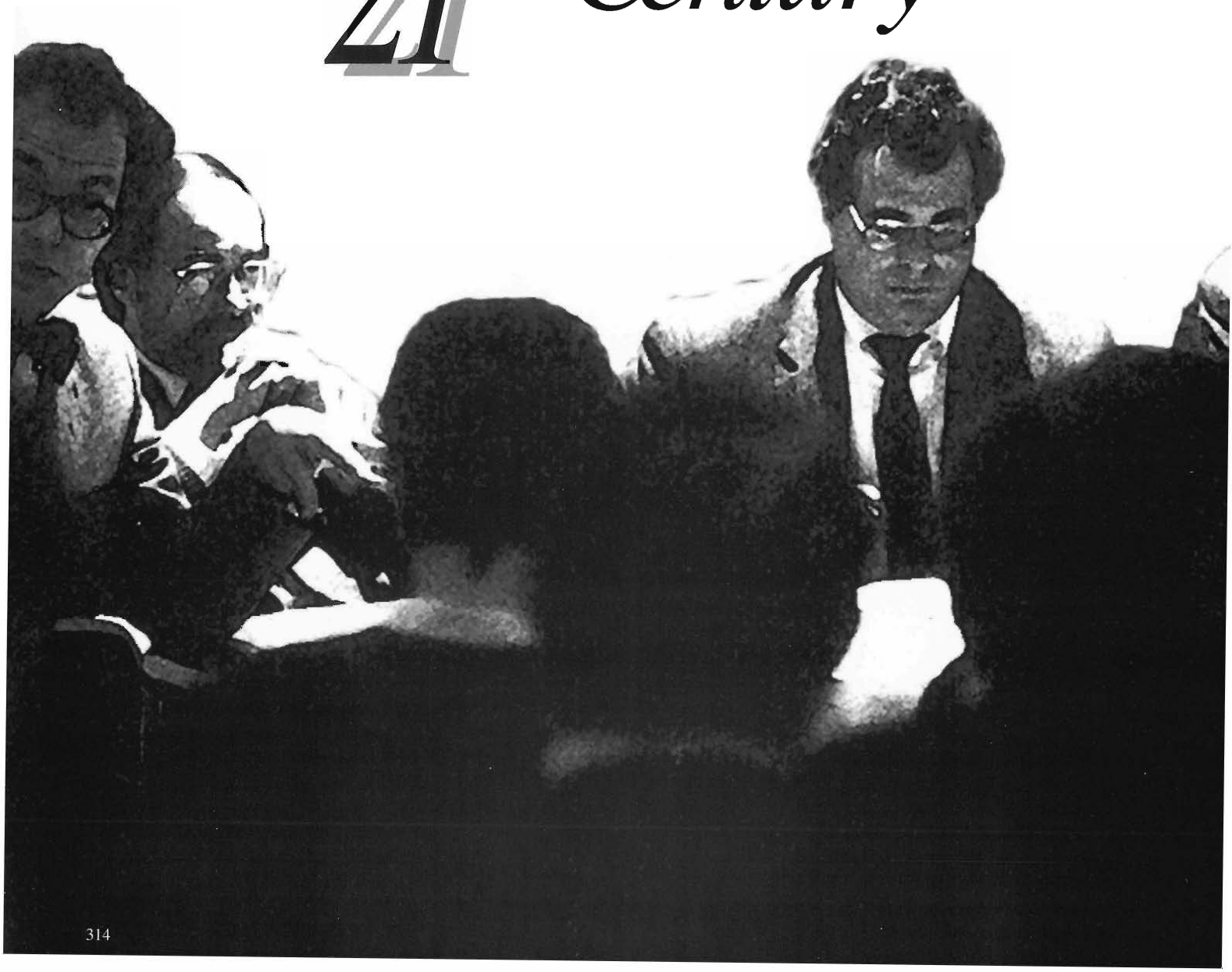
An invitation to genetics in the 21st Century



At the moment of conception, the genetic blueprint of a new life comes into being. It is an intricate message differing in slight but crucial ways from one human being to another. So far molecular biologists have decoded only a tiny fraction of this set of instructions; we live for the most part in ignorance of how our genetic inheritance will influence the course of our lives. The goal of the Human Genome Project, a fifteen-year, international research effort, is to read the entire contents of that message and to provide the tools for deciphering the genetic differences among us. Are we ready as individuals and as parents for the emergence of this new knowledge? Are we ready as a society? As a species?

At the invitation of Leon Botstein, president of Bard College, and with the sponsorship of Los Alamos National Laboratory, some of the leading participants in the Genome Project gathered at Leon's home on December 5, 1990, to answer questions about the goals and ethical implications of the project. *Los Alamos Science* offers this presentation not because the questions were all-inclusive or the answers definitive but because the issues raised, both philosophical and practical, will become more pressing as information from the Genome Project accumulates. We hope to stimulate discussion among you, your family, and your friends as we prepare to consider and act upon the resulting information with wisdom, compassion, hope, and openness.

Leon Botstein: Ladies and gentlemen, let me welcome you. The topic this evening is the Human Genome Project, and my role is to explain the format of the discussion and to introduce the panel. This is an unusual opportunity to participate in a discussion about an important issue with the people who *ought* to know what it's all about. First, David Botstein will give a somewhat brief introduction to the Project, in which he will state its goals, its history, and why he thinks it's necessary. Then, each of the panel members will be given the opportunity to make an opening statement. After that, the floor will be open to questions from the audience. I'm certain that this is not a particularly reticent panel, so there's no need for me to moderate—but rather, perhaps, to adjudicate.

Now I will introduce the panelists. David Baltimore is President of Rockefeller University. He, along with Howard Temin and Renato Dulbecco, won the Nobel Prize for the discovery of reverse transcriptase. I can't refrain from mentioning that he is a graduate of Swarthmore College, a small liberal arts college like Bard College. Next, my brother, David Botstein, Chairman of the Genetics Department at Stanford and a long-time member of the faculty at MIT. He invented the use of DNA markers and is one of the initiators of the Human Genome Project. Next is James Dewey Watson, who, together with Francis Crick and Maurice Wilkinson, won the Nobel Prize for discovering the structure of DNA. Dr. Watson is Director of the Human Genome Initiative of the National Institutes of Health and also the author of a classic book on the character of scientific discovery—*The Double Helix*. Also here tonight is Robert Moyzis, Director of the Center for Human Genome Studies at Los Alamos National Laboratory and the discoverer of the human telomere, a special DNA sequence that makes up the end of every human chromosome. Finally, Nancy Wexler, President of the Hereditary Disease Foundation and an Associate Professor at the Department of Neurology and Psychology at Columbia Presbyterian Medical College. Nancy is Chairman of the Department of Energy–National Institutes of Health joint working group on the ethical, legal, and social issues of the Human Genome Project, the group known as ELSI. I think there could not be a more distinguished and appropriate panel for this discussion.

There are many questions which were put forth by a variety of people interested in the Human Genome Project. What are the goals of the Project? What has been achieved and what might be achieved in twenty years? What are the main scientific arguments against the Project, what are the scientific arguments for the Project, and how important is it compared with other scientific projects? What are the obstacles to its success? How do scientists share the results of this project? How likely is it that the technology coming from this project will be available to physicians, hospitals, and clinics? What positive effects might come from the resulting technology? Will there be a revolution in health care? What could prevent us from taking full advantage of such benefits? What are the social effects? Why might it lead to greater social inequality, or conversely, to greater homogeneity? Is there a valid concern with respect to eugenics? Can we influence the human gene pool? Will this project affect our view of ourselves? What myths will be challenged by this research? What theological questions might be invoked by this work? Is there some issue of responsibility which might lead us not to pursue this project? Does the individual own the rights to his or her own genome? What are the legal implications? Finally, do people really want to know about their genetic inheritance? These questions are probably more than enough to generate considerable controversy. I turn the floor over to you, David.

David Botstein: One of the challenges we have not yet fully met is explaining to people who are not directly involved in the Human Genome Project what we are doing and why we are doing it. As a result, a considerable amount of misunderstanding has arisen. My purpose in this introduction is not to give you a hyper-rapid education in biology, but instead to introduce a few of the basic terms and to present the fundamental ideas around which this project is based.

First, and I'm sure most of you know this, our genes are made of DNA. It has been clear for about fifty years that, to the first approximation, all of a person's inherited characteristics are specified by the DNA of the fertilized egg. Therefore, to *understand* the entire message encoded in a person's DNA is to know everything about his or her inheritance. I did not say *transcribe* or *put on optical disk*. I said *understand*,

and a complete understanding of the message is a long way off. The big deal about a person's DNA—aside from the fact that it encodes all the information for making the person—is that it contains an extremely large number of paired nucleotide bases—six billion. Simply determining the base sequence of all that DNA is a big technical problem. In fact, determining the base sequence of *any* segment of DNA is one of the triumphs of modern biology.

For about ten years people have been able to sequence a little bit of DNA here, and a little bit there. That is, they've been able to determine the sequence of nucleotide bases for a relatively small number of genes. We know that the sequences of most genes specify proteins and that the proteins do the work in the cell. In general, however, we don't know how a particular gene and the particular protein it encodes determine a visible or measurable inherited characteristic. In this soup of six billion base pairs, the average gene, the average coding sequence for a protein, is only one thousand base pairs long, and we estimate that the human genome contains between 50,000 and 100,000 genes. So we have a very complicated technical task, first in trying to find all those genes and then in trying to understand what they do. In the last ten years it has become clear that we have the technical means to at least begin to write down the sequence of all the base pairs in the human genome. The question is: Why do it? Much of the opposition to the Human Genome Project is based on the fact that just knowing the sequence of base pairs doesn't mean anything in itself. The genetic code lets you turn the base sequence of a gene into the amino-acid sequence of a protein, but even that doesn't mean anything by current technology. It's as if you had a row of hieroglyphics and a way of transcribing them into Urdu—but you don't understand or speak Urdu. That's pretty much the situation we're in.

The next question is: How can we give meaning to the proteins that are derived from the genes? Sometimes there is a way because we've been collecting information about genes and proteins for a long time. We know globin. It's a protein that has been studied for fifty years; it carries oxygen in the blood. We know insulin, a protein that regulates the sugar in the blood. We know the sequences of the genes for these proteins. The functions of these proteins have been studied in lower organisms, such as bacteria, yeast, and mice, and a huge amount of research and manipulation has been done on these organisms. So when people found the human cystic-fibrosis gene and looked at its sequence, they said, "Aha!" because the sequence looked like the sequence of a gene that had been studied in a number of other organisms. It's called the multidrug-resistance gene, and there is a substantial literature—several hundred papers—surrounding it. When people found the neurofibromatosis gene, they again said, "Aha!" because its sequence is related to a well-known oncogene, or cancer-causing gene, and much of the biochemistry of the oncogene has been worked out in great detail. In fact, the relationship between the two genes gave a logical explanation as to what might cause neurofibromatosis tumors. So to make the discovery of genes meaningful as well as easy, we need to know the sequences of genes in experimental organisms. Yeast, for example, has genes that are very similar to those of higher organisms. However, even though the yeast genome is 250 times smaller than our own, the yeast genome has been only partially sequenced.

We have the technical means to at least begin to write down the sequence of all the base pairs in the human genome. The question is: Why do it?

The first proponents of the Human Genome Project proposed simply to go ahead and sequence the entire human genome with the current technology. Many people, including me, were appalled by this proposal because—it was stupid. A framework with which to interpret all those sequence data did not exist, and the technology then current was so slow that the job would have taken somewhere between thirty thousand and sixty thousand man-years. The Project would have wiped out biology in the same way that the space shuttle wiped out planetary astronomy. In response to this proposal, the National Research Council formed a committee that included opponents and proponents, and we drafted a set of three propositions. The first was that we begin *not* by blindly sequencing the human genome

but instead by making physical maps of it, maps similar to but on a larger scale than those that helped us find the cystic-fibrosis and neurofibromatosis genes so quickly. Included in the first proposition were proposals to improve sequencing technology so as to make it faster as well as to apply current sequencing techniques to model organisms so that we might again say "Aha!" as the human genome is being sequenced. It was also suggested that we make more detailed genetic-linkage, or co-inheritance, maps. Second, we proposed some kind of oversight by scientists of this new endeavor so that it would be neither entirely undirected research nor your Stalinist we-tell-you-what-to-do research. It's somewhere in between. It's both application-oriented and goal-oriented, but individual creativity is still applicable. And third, we proposed that a fairly substantial portion of the money be spent studying the ethical, legal, and social implications of the Project as a means of preventing us from outrunning our own thoughts and, more to the point, from outrunning those of society regarding the use of this information in ways that will benefit humankind.

Nancy Wexler: I have heard many people ask, "Can we really afford to do this project—not only in terms of the expense in time, energy, and money but also in terms of the costs for us as a society? Can we afford the ramifications of having this genetic information made available to the individual, to our insurance companies, to our employers?"

The genotype of each person here contains genetic messages indicating that at some point you are likely to develop cancer or that you are prone to heart disease, diabetes, or some other disorder. No doubt several of you have children with genetic disorders. Many of us know people with schizophrenia, or leukemia, or Alzheimer's disease, all of which have a genetic component. If, however, just as we might visit a fortune teller to have our palms read, we could go out and have our DNA read and predictions made accordingly, would we really want to know our genetic futures and the genetic futures of our offspring? Would we want to run the risk of having others know? If the health-insurance industry could predict our futures from the results of genetic testing, would we be able to get adequate insurance policies? Could we be turned down for coverage entirely? Or, if we applied for a new job, could the employer evaluate and eliminate our applications on the basis of genetic information, saying, "No, I'm sorry. You are predisposed to developing certain kinds of cancer, and we can't afford to hire you because you are too likely to increase our insurance costs." Worries such as these are not unfounded. It is a simple fact that discrimination is often economically driven, and people are concerned about what will happen to their lives when genetic information becomes available.

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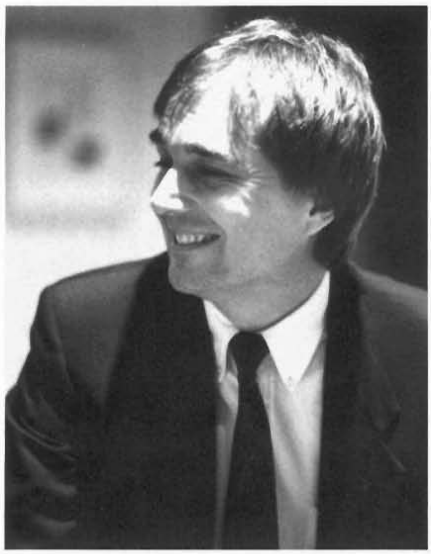
On the other hand, those of us who have been working in the field of genetic disease for a long time and who are engrossed in efforts toward finding treatments and cures, feel strongly that the question is not whether we can afford to do this project but rather whether we can afford *not* to do this project. Genetic diseases are like deadly assassins. If you are in a family at risk, you know the assassins are there, but you have no way of finding them and no way of hiding from them. The Genome Project will provide ways of finding those assassins and methods for pinning them down. It will find the lethal genetic killers as well as the genes for life–crippling disorders such as obesity and alcoholism. We'll be learning about the genes that are unique to humans and the many, many genes that we share with other species. This information will expand our understanding of our genetic heritage and enable us to have greater control over our individual lives and, eventually, better diagnoses and treatments for our genetic disorders.

There is, of course, the potential for serious misuse of genetic information both in the manner in which it is delivered to the individual and the way in which it is received by society. So, as we proceed with the Genome Project, we want to anticipate potential problems and concerns. Therefore, the DOE and NIH formed a joint working group on the ethical, legal, and social implications

of the Project. This group, informally known as ELSI, is working to develop programs and legislation to ensure that genetic information is used wisely and to the advantage—not the detriment—of the individual and society as a whole. Unfortunately, many of the concerns and issues that ELSI hopes to anticipate and address are already with us. The present situation with respect to health insurance is very disturbing. Thirty-seven million people don't have any health insurance, and fifty million are underinsured. So we need to consider *now* what will happen when the Genome Project makes possible the diagnosis of more and more genetic disorders. The high visibility of the Genome Project is, in effect, throwing a spotlight on existing problems of discrimination and social stigmatism. People are beginning to realize that almost all of us are at risk in some fashion or another, and that knowledge can give us a new impetus toward solving these problems.

Bob Moyzis: It's always a pleasure to be invited to talk about this project, one that I feel is arguably the most exciting in the history of science. We're talking about nothing less than unraveling the complete package of genetic information present in each one of your cells. In addition to accelerating the pace of identifying the genes responsible for known genetic diseases, the new information will help us to identify the genes involved in disorders like heart disease and cancer. The genetic components of these complex yet common disorders are largely indecipherable with current technology. The Human Genome Project will change that. It will form the basis for identifying many of the genes that cause the diseases that afflict mankind. As well as addressing these worthwhile pragmatic goals, this project will provide the intellectual framework for the next century of



biological understanding. We may finally understand processes as diverse as the development of a human embryo from a single fertilized egg and the

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mechanisms underlying complex human behaviors. To paraphrase what our next speaker, Jim Watson, has been quoted as saying, given the benefits that are going to come out of this project, not in two hundred years but probably in our lifetimes, I feel it's essentially unethical not to pursue it.

Jim Watson: I will explain my role in leading the NIH component of the Human Genome Project. After we recommended that the Project should go ahead and proposed a sum of money that would allow the work to be completed in a reasonable amount of time, my first

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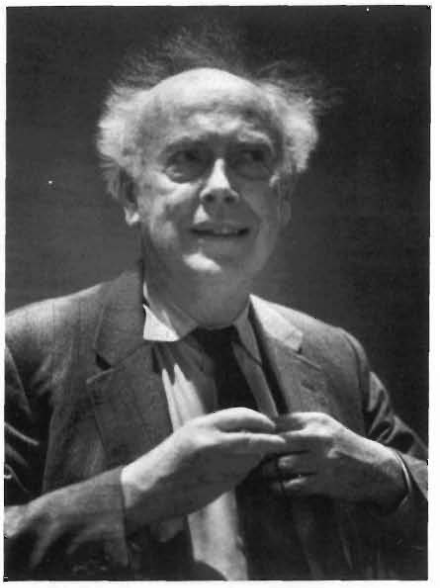
task was to assure Congress that the scientific community wanted the Project, believed it would work, and felt confident that it wouldn't be another Hubble telescope—that it was a project whose success was insured if we could get the money. The second task was to spend the money wisely. So I drafted a group of first-class scientists as advisors to the Project. I am the nominal head of the NIH component, but the real leadership comes from the advisors, who meet in formal session twice a year. We have also put together a staff of administrators within the National Institutes of Health who are really very good. People thought our project would be fun to administer. The third task, and the most important, was to persuade a group of younger people to actually *work* on the Project. We needed very bright people to put these maps together. One initial complaint was that this project's lab work was for people you wouldn't want to go to dinner with because they would have to be dull. On the contrary, the Project appeals to bright people because, if they skillfully choose their region of the genome, they may get to work on an interesting disease gene. The people working on the Project are as good as any other group working in molecular biology today. We're giving out a number of ordinary grants, but we've decided that a few people need to get a lot of money if the Project is going



to be done effectively. The Project is almost in good shape from a funding standpoint. We didn't get all the money that was initially proposed, but I think we've got enough money to fund most of the good people. We've assembled a group of highly imaginative people who are committed to the Project, and I'm actually feeling relaxed about it. The initial objections about the Project being *big* science and *unnecessary* science have been overcome. The next problem we are going to face is that of having developed predictive capabilities without having developed the cures. Who would want to have the rest of his life predicted if it can't be changed? As we find out how to predict diseases, we also have to find out how to do something about treating and curing them. That's the way to make the Project worthwhile in the best sense.

David Baltimore: I have the reputation of being a critic of the Genome Project, a role I'm not particularly comfortable with because most of what's going on is, to my mind, very appropriate and very exciting. But I can comment on it from a somewhat larger point of view because I'm neither a member of the Project nor a part of an advisory group nor a recipient of any grants. The Human Genome Project is now a great concern for all of modern biology because the maps being made will help find *all* genes, not only those that cause disease, but those that do all the normal things. To a large extent, we are what we are because of our genes. In order to discover all the genetic blueprints that determine what we are and to understand how we came to be what we are, we need the Human Genome Project. But this project as it stands today is a very small piece of modern biology. The Genome Project is being funded at $100 million a year, whereas *$8 billion* a year of NIH money is spent on health research. Molecular genetics, modern genetics, molecular biology—all of these words subsume an incredible ability, evolved over the last fifteen years, to gain an understanding of the workings of all of the systems of the body. The Genome Project will help to bring together disparate attempts in laboratories around the world to find out how kidneys work, how livers work, how a fertilized egg develops into a human being—or into a tree sloth. I support the Human Genome Project in its *human* focus because there are a whole range of things that are particularly human, and we have to study them within our own DNA if we are ever going to understand our learning processes, our behavioral processes, and ultimately our ability or inability to work together to form a society. In a broad sense the Human Genome Project represents an attempt to do all of these things.

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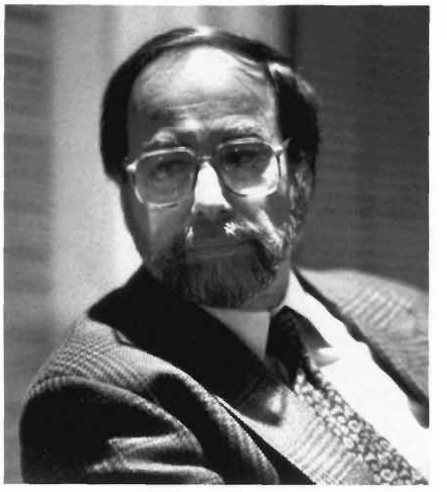
There are, inevitably, ethical problems arising out of the works of modern biology, but they don't necessarily relate to the Genome Project alone. We are



delving into ourselves. We have lived with a myth about ourselves for a very long time, and that myth is that we are all equal, all the same. It's a myth with very potent political and social implications and a myth we ought to believe as long as we have nothing else to believe in. The Genome Project is going to teach us that we are not all the same, that we are all different in ways we could never have understood before. We are going to have to come to terms with the fact that we are all born with different talents and tendencies. It is my belief that knowledge brings freedom and that knowledge of ourselves will bring us freedom from potential disease, from the potential inability to learn, and from the potential inability to cope with certain aspects of modern society. We need to know not just what it is that makes us human beings, but what makes

us *particular*, *individual* human beings, and the Genome Project is a piece of the development of that understanding, a piece we need to support. When we contemplate the ethical challenges that lie ahead, we need to examine not only the Human Genome Project, which is a paper tiger in many ways, but also the overall capabilities of modern biology. I ask you to consider whether you agree with me that this kind of knowledge represents freedom.

Questions & Answers

Question: *From a layman's point of view, one of the most interesting things about this massive science project, perhaps unlike others in the past, is that it is taking on from the very beginning the questions of its own implications for human beings. How are you going to examine the legal, ethical, and social aspects of this project?*

Nancy Wexler: Jim Watson is responsible for initiating the formal structure within the Human Genome Project to anticipate and address those issues. The development of such a program made some people nervous. They said, "Well, the ethical issues will take care of themselves as we go along." But Jim thought those issues should be explored and addressed as an integral part of the Genome Project. So he went ahead and created a working group that is now jointly sponsored by the Department of Energy and the National Institutes of Health. Both organizations have designated a portion of their total budgets for the Genome Project for the examination of the ethical, legal, and social implications of the Project, thereby creating the largest biomedical-ethics budget anywhere in the country.

The funds are being used to support a large number of activities. The joint NIH-DOE ELSI working group, which meets four times a year, hopes to stimulate public discussion as well as help develop policy options that assure that the knowledge the Project generates will be of maximum benefit to individuals and to society. ELSI has identified four high-priority areas for program activities: quality and access in the use of genetic tests; fair use of genetic information by employers and insurers; privacy and confidentiality of genetic information; and public and professional education. We've organized conferences and workshops, and we are supporting a variety of research projects related to this topic. We are looking at existing legislation and perhaps will develop model legislation and model policy. The visibility of the Genome Project has meant that certain penchants for discrimination have been opened to public scrutiny in a way they have never been before.

Bob Moyzis: I think it's important to emphasize that by setting aside a percentage of the genome budget for ELSI activities, we will not be able to miraculously decide all of the ethical issues associated with this project. We hope instead to catalyze exactly the type of discussion we are having tonight. We all hope that society as a whole will come to a realistic and positive consensus on the solutions long before the problems are permitted to materialize. We live in a democracy. All of us should be involved in deciding how we want to deal with the inevitable problems.

Question: *You have suggested that studies of DNA will reveal ethnic differences, personality differences, psychological proclivities, and so on. Is that true? Will such studies reveal why two brothers, for example, David and Leon Botstein, have gestures that are very similar?*

David Botstein: Frankly, we don't know the answer to that question. Maybe our gestures are our mother's gestures, and we learned them from her, or maybe we inherited them from her—right now we can't tell. I think, however, that we are going to find out that in some cases our behavior is inherited and in other cases it is not, and we have to learn to live with that fact. Common sense already tells us that. But in my view genetic facts don't change your rights. The idea that we are all equal means we all have equal

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rights, not equal abilities. The fact is I could never have been a professional basketball player—I simply wasn't tall enough.

Leon Botstein: *That's* not the reason.

David Botstein: That was among the very many reasons. On the other hand, certain skills or abilities are easily improved by training. Take running, for example. Even unselected people can run. They may run much more slowly than their potential, but if they train hard, eat the right stuff, and learn how to get down on the blocks and anticipate the starter's gun, they will run faster. It will be extremely difficult to sort out the genetic component of such skills even if we are able to follow all of the genes involved. Some people will be very smart or very athletic because they study or train, and others will be up at the same level due to natural talent. Separating the two components is not a matter of genetic technology alone. It's difficult, and for some abilities it's never going to happen. So while we will be able to figure out the genetic component for a lot of these personal traits, it's very unlikely that we will be able to predict with certainty whether a person will be smart or be a fast runner without regard to factors such as education and training.

Question: *In his opening statement David Baltimore said the knowledge resulting from the Genome Project will bring freedom, but knowledge also brings responsibility and choice. Suppose prenatal testing reveals a genetic propensity toward alcoholism or low IQ or something else that the parents may simply not want to settle for even though it is not a disease. Will the parents be allowed to say, "We do not want this being ever to come into existence"? Can society eventually determine that certain qualities disappear? We can already do that to some extent, but if it's a question of IQ, what will happen?*

David Baltimore: There is no question that along with knowledge and the freedom of choice will come very difficult social and political questions that have major moral aspects and that don't have a right or wrong answer. As our knowledge of human genetic variability deepens, the opportunity to avoid more and more traits in our offspring will present itself. It is very doubtful that we will see the disappearance of specific traits, but individuals will have a wider range of choices. To me, it is much more important that by understanding the inheritance of an individual we can help that individual develop his or her maximum potential. This may mean tailoring the individual's education both to take advantage of strengths and to compensate for weaknesses. It may mean counseling an individual to take directions in life that build on inborn capabilities.

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Jim Watson: I would prefer to trust the individual rather than the state in that sort of decision. Some people feel very strongly that sex selection shouldn't be allowed, but I would have compassion for parents who already had eight boys and wanted a girl. I would personally be very frightened by any political control that took the power away from parents. I shudder at the thought of state control over this issue. The laws would necessarily be imperfect.

David Botstein: I would like to point out the following simple-minded numerical facts about designing the make-up of future generations. When you pass on traits, you pass them on in a binary way. The father's sperm decides whether an offspring will be a boy or a girl. That means half the fertilized eggs will be boys, so if you choose boys you already have only half of the fertilized eggs to choose from. If you make another binary choice, you have a quarter of the eggs to choose from. If you have yet another binary choice, it's an eighth. If the array of basketball-playing genes is thirty, then only one out of over a billion of the embryos has them all, and that's a prohibitively low fraction. So choosing a genotype for anything complicated is, in principle, extremely impractical. It's just not likely to happen. The moral problem is there whenever you choose one embryo over another, but this business of specifically designing your offspring in one fashion or another—forget it!

Leon Botstein: David, the popular myth is not so much being able to choose among embryos but being able to make changes in a given embryo.

David Botstein: Genetic information will permit you to identify, in part, what's going to happen to an individual. That's a prerequisite to manipulation, but it's not nearly sufficient, and manipulation, at least manipulation of egg and sperm cells, is very, very far away. What you can do is choose from among the available embryos and, as I said, it's unlikely that there will be much of that. In fact, I expect there will be none.

Jim Watson: I'd like to make a point. Eugenics is supposed to be a bad word that we sort of equate with Hitler. It says we are trying to determine or change the nature of the human germ plasm. The most repulsive aspect about the eugenic efforts both in this country and, in particular, in Germany is that eugenic choices were made by the state, often on the basis of very incomplete knowledge. In this country we had a sterilization program that involved about twenty thousand women who were judged to be feeble-minded solely on the basis of their being prostitutes. This program was carried out in the 1920s and 1930s, and the people who were sterilized had no choice in the matter. The matter went to the Supreme Court, where a decision was made in favor of the sterilization program. The jurist most responsible for the decision was Oliver Wendell Holmes, who said that the state had the right to improve its future citizens. Then when we saw what happened in Germany, we decided that eugenics was extremely bad. On the other hand, to say that you can't really make choices to eliminate a gene for Duchenne's muscular dystrophy, to say that you want to perpetuate that gene for your descendants, is to be *mad*. That gene brings total and absolute agony upon your descendants. If you have the option of having children without that gene, you might certainly want to choose that option. That's my opinion. Likewise, if you know you are a member of a cancer-prone family, and there are means by which you can have children who would not possess this trait, I think you as parents should have the opportunity to make that choice. I think it would be absolutely dangerous for anyone else, especially the state, to make such decisions. To say that parents must perpetuate things that bring only agony upon themselves and their offspring appears to me to be terribly immoral. No one should be allowed to prevent us from improving our own individual lives and the lives of our children.

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Question: *David Baltimore pointed out the myth of equality. But we're fortunate that in our political system, in our culture, in our institutional arrangements, we* try *to assure equality of* opportunity *in a wide variety of ways. But there is another kind of myth deep in our Western culture, and that is the notion that we are volitional animals, that we have a capability to choose how we act, appropriately or inappropriately. I do not object to the Genome Project on this ground, but it seems that we are heading toward challenging a fundamental precept of our society as we unfold the dynamics of behavior by means of our growing understanding of genetic inheritance. I wonder whether some of the opposition to the Genome Project might stem from a fear that the results of the Project will show that we are not in fact volitional animals and do not really have free will.*

Jim Watson: I have not met anyone who does not believe he has free will, the ability to make choices. But we will not really know what that means until we understand how our brains function, and that is a long way off. Nevertheless, if we eventually do understand how they function, I will be very surprised if we feel any differently. If you are born into a given political or cultural tradition, there are pressures to stay in that tradition. My political views are pretty similar to my parents' political views, and so traditions are passed on. We might say that I don't really have the freedom to be a Republican, but actually I do. So I don't think the Genome Project is going to touch the free-will issue.

Question: *When you say that the gene that causes cystic fibrosis is somehow abnormal, I think we are all with you. But in the case of behavioral or learning processes, how do you decide what the*

healthy or normal gene is? Is there a way of defining normal *by more valid means than merely by accepting society's viewpoint?*

David Botstein: That's a good question. I don't know what's normal. In dealing with species other than ourselves, we have an operational definition of normal. Normal is what you find out in the wild. It's called wild type. If you catch a fly and it has certain characteristics, that's wild type, that's normal. Any differences are not called mutations or diseases, they're called polymorphisms, a neutral term, right? The point is that when people die horrible deaths due to their genetic content, we say disease, but we might simply view it as a variation of what you would call wild-type human.

David Baltimore: You say there are normal and polymorphic variants, but that's not really correct. There is no normal. They are all polymorphic variants.

David Botstein: That's right. I stand corrected.

David Baltimore: I learned it from you so I know it's right. There is a range of variations we consider normal and there are those outside that range that we consider abnormal. Things like cystic fibrosis are clearly diseases, but we have to be very conscious of the fact that in any gene we will see a very wide range of variation and that most of that variation is normal.

Nancy Wexler: Even in terms of a single disease the variation can be very great, and variations in the symptoms and progression of the disease make counseling very difficult. For example, one child with cystic fibrosis will die at age four and another will still be living at age fifty. It's hard to consider options and make choices when the effects of the disease are so unpredictable.

Bob Moyzis: That's an important point. One of the more immediate impacts of this project that we all hope to see is a more individualized approach to health care. Complex human diseases like heart disease, for example, are likely to

be the result of a combination of many genes. Nevertheless, you are treated like the generic human being, and the doctor tells you the fifteen things that you should do to lower your cholesterol. The new information will free us from this idea that we're all the same, and you'll get much more individualized medical treatment. In five or ten years you will be able to walk into your doctor's office and the doctor will take a little bit of blood, get an analysis of a variety of genes, and be able to personalize your treatment. Maybe you will be able to eat all the eggs that you want because it's probably not going to matter whatsoever, but you better avoid, say, jogging ten miles per day because it's probably going to kill you. I say *probably* because for complex things like heart disease, it is doubtful that we will ever be able to say with real certainty that if you do this or that you'll be free of the disease.

Question: *You said you have received a great deal of funding for this very difficult technical project, but I think the ethical aspects are even more difficult. I'm interested in knowing how they will be addressed. How will they be funded and how is that money going to be spent?*

Nancy Wexler: The efforts to evaluate the ethical, legal, and social implications of the Genome Project are as much a part of the Project as the efforts to construct the maps. ELSI's activities go hand in hand with the development of the basic science because it's critical that our discussions, workshops, research and conference grants, and efforts toward policy development be grounded in the capabilities and limitations of both current and future technology. David's calculations show that it's unlikely that we'll see many people going into their obstetrician's or gynecologist's offices to sort through embryos and pick out their favorites. People talk about these kinds of horror stories, but technically and practically, I doubt it will be our top problem. At this point we are trying to clarify the issues and assess the most

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salient ones through discussions of the kind we're having right here. What are people really concerned about? What do people see as the issues for them? Are there issues of which we are unaware? A group of seven research teams around the country, managed by ELSI, has undertaken a three-year study to evaluate the benefits of making a test for the cystic-fibrosis gene available to the public. The study will also develop and assess methods for educating and counseling people who want to be tested for this gene. We hope the findings will supply health-care professionals with strategies that maximize a person's understanding of genetic testing as well as record-keeping and disclosure policies that will best protect the individual against breaches of confidentiality, stigmatism, and discrimination. ELSI has also established an Insurance Task Force working toward developing guidelines

for insurance policy by 1993, and we have commissioned a White Paper to delineate policy options in the area of genetic testing relative to insurance and employment. Funding also goes toward individual research grants, conference grants, and post-doctoral fellowships designed to address the entire range of ethical, social, and legal implications of the Project. The ELSI Working Group has carefully evaluated the Americans With Disabilities Act and outlined suggestions for the improvement of the Act relative to genetic issues such as discrimination and privacy. ELSI also sponsors public outreach meetings in order to encourage community discussions. We hope to educate the public and stimulate community interest and involvement in the process of shaping future policies.

Question: *You have a lot of big names working on this project, and they have drawn an enormous amount of funding, congressional and otherwise. How will this project affect other areas of science where funding might be somewhat reduced?*

Jim Watson: The money spent on the Genome Project is going to make other aspects of biological science more efficient by bringing them out from under an umbrella of complete ignorance, similar to the one that shrouded cancer research before the discovery of oncogenes. A lot of money is now being spent on trying to alleviate terrible medical conditions. People go to Congress, and Congress votes money in an attempt to help. For example, one of the best things we can do to address the problem of aging is to try to find the genes that predispose one to Alzheimer's or other forms of abnormal aging. By doing that we'll gain real scientific clues as to what is going on and what we can do to help.

Question: *First, could you share with us the three or four most difficult confidentiality questions related to the Genome Project? Second, I can imagine a time when boy meets girl and there's an added dimension, the genetic cost. The two might be a perfect match until they check to see if they have matching cystic-fibrosis cards. Is that where we're headed, everybody carrying around their own genetic ID card? Third, Dr. Watson, you said everyone has free will, but does everyone have the same capacity to exert their will? And is that capacity detectable through genetic testing? Is it associated with a gene? And if it is associated with a gene, then what does that mean for those who don't have the capacity to exert their will?*

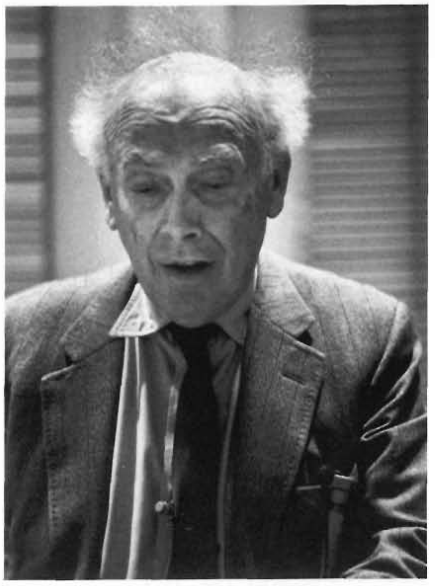
Jim Watson: You have cited several ethical problems that need to be addressed, but the most critical of them—and you referred to it indirectly—is what I call genetic injustice. DNA replication

No matter how it may upset the insurance companies and the employers, confidentiality has to be a guaranteed right.

isn't perfect, so some people are born with genes that do not work properly. People are either slightly disabled or greatly disabled depending on what gene function is impaired and the extent of that impairment. Everyone knows that people are different from one another, and it's been convenient to ascribe those differences to our environments, to the fact that we didn't have certain opportunities in our childhood, or we didn't have a good education, or we didn't see a doctor when we should have, and so on.

In our rational society we think we can pass laws to correct the inequalities

resulting from man's environment. We can do away with poverty. We can do away with all the things that clearly make people unequal. But now we know that certain kinds of inequality come from our genes. A paper on early-onset breast cancer identifies a gene on the short arm of chromosome 17 that predisposes women to breast cancer.



Women who inherit that gene are going to have a much greater probability of having breast cancer than other women. That's terribly unjust, there's nothing nice about it, but it's true. How do we cope with that inequality? Do we tell people to have tests so they can find out if they have that gene? Do people really want to know? Would it be better if everyone thought they were equal, that it's God's will if they get cancer?

Some call New Jersey the Cancer State because of all the chemical companies there, but in fact, the major factor is probably your genetic constitution. If you were lucky enough to have both your parents live to be one hundred, you're probably going to live a long life. Basically the inequality comes from our genes, and what we have to do is try to find cures and treatments so that we can circumvent the inequalities.

Our knowledge of some diseases is improving so quickly that such hopes are not completely unrealistic. In other cases, science won't be able to come to the rescue. In those cases genetic information *must* be confidential. We shouldn't be stamped as unequal due to our genetic heritage. No matter how it may upset the insurance companies and the employers, confidentiality has to be a guaranteed right. For example, no presidential candidate should be able to say, "*I* will let my genes be seen by everyone," thereby forcing his opponent to come out with what might be construed as damaging genetic information. The need for confidentiality is paramount. We must try to treat and cure as much genetic inequality as we can, but it exists and we've got to live with it.

David Botstein: Jim proposes to make genetic information so confidential that nobody but the individual can know anything. The better solution would be to have health insurance guaranteed for everyone. Then the injustice of having the wrong genes would not be compounded by the injustice of not having any health care, which is where we seem to be heading in this country. If we solve the insurance problem, then I believe there will be no pressure for genetic testing. Usually health insurance is the issue.

Nancy Wexler: We as Americans feel that we are *legally* entitled to greater confidentiality than is actually granted us by law. We're now looking at the extent to which existing laws protect against violations of confidentiality. The genetic privacy issue is complicated because laws vary from state to state just as record-keeping methods and disclosure policies vary from one health-care provider to another.

Another complication arises from the fact that our genomes are inherited from our parents and passed on to our children. That simple fact means that *personal* information about one individual's genome will often yield information about that individual's parents, siblings, or children. It's like pulling a thread on a sweater—one tug and a whole string of aunts, uncles, and cousins begins to unravel. We want the use of genetic testing to be a positive development in a health-care environment where privacy is assured, but there may be situations where absolute respect for an individual's genetic privacy could be detrimental to their relatives' health. ELSI is working to develop policies that will help satisfy questions about the ownership and control of genetic information as well as matters of consent to disclosure and use of such information. It's a complex issue, but we need to keep in mind the fact that the real attraction of the Genome Project lies in the hope that by understanding disease genes we can develop treatments. Before we had the

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ability to detect disease genes, the only way a couple could find out whether they had the *matching cards* mentioned earlier was to *have* an affected child, and then they had that agony to face. One of the benefits of having a genetic test for breast cancer, for example, is that it allows for early detection and

treatment and the ability to save many, many lives.

David Baltimore: The questions about confidentiality and testing may be the most difficult issues facing us at this time. In the long run, however, I expect this concern will probably dissipate and eventually disappear. As we learn more, we will discover that all of us have some deleterious aspects in our inheritance, and the only means of having a work force at all will be to dismiss the concept of the perfect person for the perfect job. However, I hope that long before we come to that conclusion, we will have put the responsibility not on the individual but on the insurance companies and the employer. We have health insurance so as to share health risks, and one of the rights an individual has is the right to work in the profession of his or her choice. I'm uncomfortable about psychological testing, and I am *very* much opposed to genetic testing as a basis for granting or denying employment or insurance.

Question: *Who will take care of the confidentiality of the genes of an embryo? Is it possible to protect it? If it's possible in the United States, is it also possible in India or Argentina?*

David Botstein: The problems in India and Argentina are very serious, and I doubt that any massive amount of genetic screening will be done. Many countries still have trouble getting *vaccinations* done.

Nancy Wexler: Nevertheless, let's recognize the fact that they had to pass a law in India against sex selection because parents were using genetic screening to avoid having female offspring.

David Botstein: That sort of problem is self-correcting.

Nancy Wexler: Yes! It's *definitely* self-correcting. Most geneticists never intended their scientific work to be used for anything other than the detection of serious diseases. In certain situations, however, it is necessary to institute laws or use social policy to prevent *other* people from using scientific knowledge for purposes beyond those which the geneticists had envisioned.

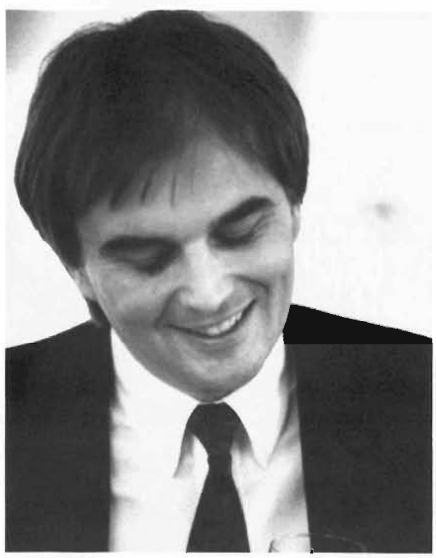
Question: *If we use genetic information to select against certain disease genes, such as cystic fibrosis, by choosing the good eggs and avoiding the bad ones, will our gene pool be depleted?*

The question is: Can you eliminate genes from the population? The answer is: No.

David Botstein: The question is: Can you eliminate genes from the population? The answer is: No. There is a simple numerical argument. Cystic fibrosis is a recessive disease, so only people with two CF genes, we call them homozygotes, are affected with the disease. But most CF genes are in *hetero*zygotes, people with one normal gene and one CF gene. These people are carriers, but they exhibit no adverse symptoms and therefore are not selected against. Since they are not selected against—and why should they be?—the CF gene will always remain within the population.

Question: *Would that be true for dominant genes as well?*

David Botstein: No, it is not true for dominant genes. But there are very few prevalent dominant genes for serious diseases except those that are *new* mutations. Dominant disease genes tend to fall by the wayside because of their dominance. People who are afflicted with the worst dominant diseases usually don't live long enough, or they're simply unable, to bear offspring.



Bob Moyzis: The question concerning the gene pool raises a very critical point, namely, that all species, humans

included, benefit from great genetic diversity. It is essential for our survival and future adaptability. Although some have imagined that genetically homogeneous societies would have advantages, true homogeneity would be a death sentence. Environments change, including social environments, and a species that cannot adapt will be eliminated. No matter how much we learn about the human genome over the next hundred years, there will always remain many things that we do not understand or cannot predict, such as who will be a great artist. It's not clear we will ever figure out the genetic components of complex human traits such as creativity. If you select against a particular gene, you may be eliminating something else that we deem valuable but the origins of which we don't yet understand.

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Jim Watson: A case in point might be the genes which predispose people to manic-depressive psychosis—finding those genes is an objective of the Project. We want to find a treatment that will be better than lithium since some cases don't respond to it, nor to any known drug. We're thinking the Project may be the best way of finding out what goes wrong. On the other hand, we might want to pause and wonder what our society would be like *without* manic-depressives—

Nancy Wexler: The room would be empty!

Jim Watson: It is a disease which can bring great suffering, but it can also bring great fortunes. Manic-depressives can do things that others say cannot be done. So it's a case where it's not obvious that we're dealing with a *bad* gene.

Leon Botstein: We would almost certainly lose our great poets.

Question: *Suppose you find a genetic propensity for something like aggression, which affects other people as well as the individual. How would you cope with that? Do you leave all of society naked and exposed to a person who might be dangerous?*

Jim Watson: I think that's the sort of ethical question that you can't really deal with until you've shown that such a genetic propensity exists. Even if you could, how would you use the information? Most good scientists, for example, are terribly aggressive.

Question: *I am not really completely comfortable with the scientific aspects of what we have discussed, but it seems to me that there are really two issues. One we would all vote for, namely, the issue of diseases; and one we would all vote against, that is, the issue of personality traits, such as IQ. We're spending this country's fortunes so as to make learning about our genes a lot easier. Are we going to learn more about these somewhat vague personality traits or more about these lethal diseases?*

It seems . . . that there are really two issues. One we would all vote for, namely, the issue of diseases; and one we would all vote against, that is, the issue of personality traits, such as IQ.

David Botstein: I believe we will understand diseases much earlier than personality traits because diseases are much better defined. We haven't really defined personality traits precisely enough to correlate them with genetic information. So diseases will probably come first.

Question: *Do you suspect the ethical considerations will have to broaden in order to be relevant to other cultures and other societies? Tonight, the answers about confidentiality seem to relate back to our society, which values individual rights and has insurance. But the transfer of this technology to cultures that don't have notions of individual rights,*

much less insurance for individuals, might have very serious repercussions.

Nancy Wexler: That is an important issue. People are concerned about giving diagnostic probes to China, for example. Should we give diagnostic testing capabilities to countries where counseling is not likely to accompany the tests and where confidentiality rights are not guaranteed? Through an international organization called the Human Genome Organization, which has an ethics working group, we try to collaborate with other countries in order to emphasize the importance of providing those services and protections.

Question: *What is the time frame in which you hope to accomplish the Genome Project?*

David Botstein: The high-resolution genetic-linkage map and the sequences of some of the model organisms are both parts of our five-year goal, as is a great majority of the physical map. The human-genome sequence itself is, essentially, not one of the five-year goals. The expectation is that it will be completed in approximately fifteen years.

Jim Watson: Within the next five to ten years we want to get all the tools needed by the disease-gene hunter, the person who wants to find, say, the Alzheimer's gene. We are in a hurry to get them. That's our impatience. We say in five years, maybe ten, the last bits of that resource will be put together. We are in a hurry. ■

Photos by G. Steve Jordan, New York